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For the Patent- and Registration Office

A. Södervall

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NOVEL COMPOUNDS

The present invention relates to substituted piperidine compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

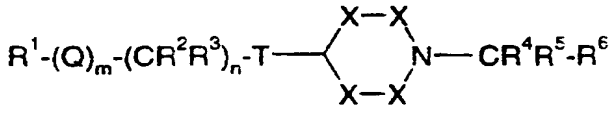
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

In accordance with the present invention, there is therefore provided a compound of general formula

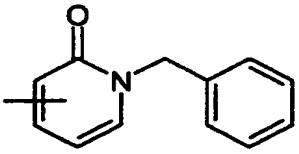


(I)

wherein

R^1 represents a C_1-C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio and C_1-C_6 alkoxycarbonyl, or

R^1 represents a 3- to 10-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from halogen, cyano, nitro, hydroxyl, carboxyl, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylthiomethyl, C_1-C_6 alkylcarbonylamino, $-NR^7R^8$, $-C(O)NR^7R^8$, C_1-C_6 alkylcarbonyloxymethyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonylpiperazinyl, furyl, phenyl, pyridinyl, pyrazinyl, halophenyl, thienyl, thienylmethyl, C_1-C_6 alkylbenzyl and



;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR^9, C(O), $C(O)NR^9$ or $NR^9C(O)$;

n is 0, 1, 2, 3 or 4, provided that when n is 0, then m is 0;

each R^2 and R^3 independently represents a hydrogen atom or a C_1-C_4 alkyl group;

T represents a group NR^{10}, $C(O)NR^{10}$ or $NR^{11}C(O)NR^{10}$;

each X independently represents a group CH_2, CHR^{12} or C=O, provided that at least two groups X simultaneously represent CH_2;

R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_4 alkyl group;

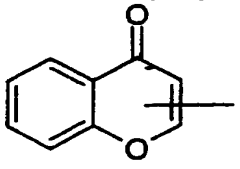
R^6 represents a phenyl group optionally substituted by one or more substituents independently selected from halogen, amino ($-NH_2$), nitro, cyano, sulphonyl ($-SO_3H$), sulphonamido ($-SO_2NH_2$), C_1-C_6 alkyl, C_1-C_6 haloalkoxy and C_1-C_6 alkylsulphonyl;
R^7 and R^8 each independently represent a hydrogen atom or a group selected from C_1-C_6 hydroxyalkyl, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by phenyl;
R^9, R^{10} and R^{11} each independently represent a hydrogen atom, or a C_1-C_4 alkyl or cyclopropylmethyl group; and
each R^{12} independently represents a C_1-C_4 alkyl or cyclopropylmethyl group;
or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated an alkyl substituent or an alkyl moiety in a substituent group may be linear or branched. Examples of alkyl groups/moieties containing up to twelve carbon atoms include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl and n-dodecyl groups. A C_1-C_6 hydroxyalkyl group will comprise at least one hydroxyl group (e.g. one, two or three hydroxyl groups) which may be attached to an internal or terminal carbon atom of the alkyl chain. Similarly, a carboxy-substituted C_1-C_6 alkoxy group will comprise at least one carboxyl group (e.g. one, two or three carboxyl groups) which may be attached to an internal or terminal carbon atom of the alkyl chain. A C_1-C_6 haloalkyl or C_1-C_6 haloalkoxy group will comprise at least one halogen atom (e.g. one, two, three or four halogen atoms independently selected from fluorine, chlorine, bromine and iodine) which may be attached to an internal or terminal carbon atom of the alkyl chain. A halophenyl group will comprise from 1 to 5 halogen atoms independently selected from fluorine, chlorine, bromine and iodine. A C_1-C_6 alkylbenzyl group will comprise at least one C_1-C_6 alkyl group (e.g. one, two or three C_1-C_6 alkyl groups) attached to the phenyl ring of the benzyl moiety. If there is more than one C_1-C_6 alkyl group attached to the phenyl ring, the groups may be the same or different. In a C_1-C_6 alkoxycarbonylpiperazinyl substituent group, the piperazinyl moiety is attached through a nitrogen atom to the carbonyl moiety. When T represents $C(O)NR^9$, it should be

understood that the nitrogen atom is attached directly to the six-membered heterocyclic ring in formula (I).

The group R^1 may represent a C_1-C_{12}, preferably C_1-C_{10}, more preferably C_1-C_6, alkyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from cyano, hydroxyl, C_1-C_6, preferably C_1-C_4, alkoxy, C_1-C_6, preferably C_1-C_4, alkylthio and C_1-C_6 alkoxycarbonyl, preferably C_1-C_4 alkoxycarbonyl.

The group R^1 may alternatively represent an optionally substituted 3- to 10-membered saturated or unsaturated ring system which optionally comprises one or two ring carbon atoms that form carbonyl groups and which optionally further comprises one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of ring systems that may be used which can be moncyclic or polycyclic include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyrazolyl, furyl, thienyl, imidazolyl, quinolinyl (e.g. 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), pyridinyl (e.g. 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), 1,3-benzodioxolyl, thiazolyl, benzimidazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl), triazolyl (such as 1,2,3-triazolyl or 1,2,4-triazolyl), benzothiazolyl, pyrimidinyl (e.g. 2-pyrimidinyl or 4-pyrimidinyl), benzothienyl,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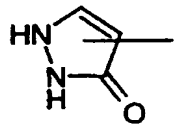
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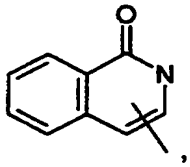
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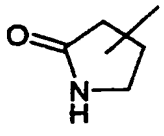
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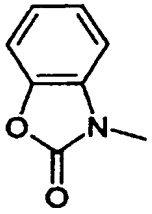
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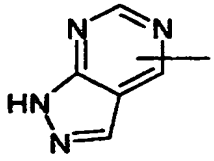
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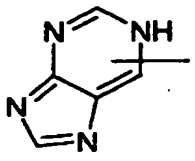
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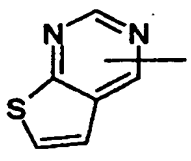
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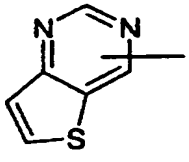
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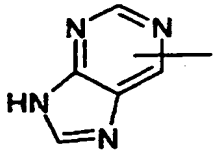
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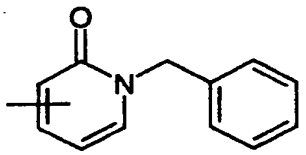
The ring system of R^1 may be optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine); cyano; nitro; hydroxyl; carboxyl; C_1-C_6, preferably C_1-C_4, alkyl (especially methyl or ethyl); C_1-C_6, preferably C_1-C_4, hydroxyalkyl; C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl); C_1-C_6, preferably C_1-C_4, alkoxy (especially methoxy, ethoxy, n-propoxy or isopropoxy); carboxy-substituted C_1-C_6, preferably C_1-C_4, alkoxy; C_1-C_6, preferably C_1-C_4, alkylthio (especially methylthio, ethylthio, n-propylthio and tert-butylthio); C_1-C_6, preferably C_1-C_4, alkylthiomethyl (particularly methylthiomethyl); C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (especially methylcarbonylamino); $-NR^7R^8$; $-C(O)NR^7R^8$; C_1-C_6, preferably C_1-C_4, alkylcarbonyloxymethyl (particularly methylcarbonyloxymethyl); C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (especially methoxycarbonyl or ethoxycarbonyl); C_1-C_6, preferably C_1-C_4, alkoxycarbonylpiperazinyl; furyl; phenyl; pyridinyl; pyrazinyl; halophenyl (especially chlorophenyl); thienyl; thienylmethyl; C_1-C_6, preferably C_1-C_4, alkylbenzyl (particularly methylbenzyl); and



Preferably, Q represents a sulphur atom or a group NH, C(O) or NHC(O).

Preferably T represents a group NH, C(O)NH or NHC(O)NH.

Preferably, all four groups X represent CH_2.

It is preferred that each R^2 and R^3 independently represents a hydrogen atom or a methyl group, especially a hydrogen atom.

R^4 and R^5 preferably each represent a hydrogen atom.

R^6 represents a phenyl group optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), amino, nitro, cyano, sulphonyl, sulphonamido, C_1-C_6, preferably C_1-C_4, alkyl, C_1-C_6, preferably C_1-C_4, haloalkoxy and C_1-C_6, preferably C_1-C_4, alkylsulphonyl.

R^6 is most preferably a phenyl group substituted by halogen.

R^7 and R^8 each independently represent a hydrogen atom or a group selected from C_1-C_6, preferably C_1-C_4, hydroxyalkyl, C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) and C_1-C_6, preferably C_1-C_4, alkyl optionally substituted by phenyl (e.g. one or two phenyl groups).

Most preferably, R^7 and R^8 each independently represent a hydrogen atom, or a group selected from C_2 hydroxyalkyl, cyclopropyl and C_1-C_2 alkyl optionally substituted by phenyl.

Particularly preferred compounds of the invention include:

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methylbenzyl)amine,

N-[4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenyl]acetamide,

3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenol,

N-[(4-Chloro-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-furyl)methyl]amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-nitrobenzyl)amine,

N-Benzyl-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-fluorobenzyl)amine,

N-(2,6-Dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N,1-Bis(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-pyridinylmethyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(3-methyl-2-thienyl)methyl]amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-thienyl)methyl]amine,
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methoxyphenol,
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol,
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-4H-chromen-4-one,
N-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[(4-Chloro-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-{[1-(4-methylbenzyl)-1H-pyrazol-5-yl]methyl}amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(2-phenyl-1H-imidazol-4-yl)methyl]amine,
N-[(2-Chloro-3-quinolinyl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(6-methyl-2-pyridinyl)methyl]amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-quinolinylmethyl)amine,
[5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-furyl]methyl acetate,
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-pyridinylmethyl)amine,
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol,
N-[2-(tert-Butylsulfanyl)benzyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-ethylbenzyl)amine,
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxybenzoic acid,
N-(1,3-Benzodioxol-4-ylmethyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(1,3-thiazol-2-ylmethyl)amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-ethyl-2-furyl)methyl]amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-quinolinylmethyl)amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-quinolinylmethyl)amine,
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxy-3-methoxybenzoic acid,
N-[(4-Bromo-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,

2-[2-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6-methoxyphenoxy]acetic acid,

N-[(4-Bromo-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-iodobenzyl)amine,

3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6,7-dimethyl-4H-chromen-4-one,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-isopropoxybenzyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-methylbenzyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-pyridinylmethyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2,4-dimethylbenzyl)amine,

Ethyl 5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methyl-3-furoate,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-furamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]butanamide,

2-{[5-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-6-methoxy-4-quinolinecarboxamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-furyl)-4-quinolinecarboxamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butanamide,

3-(1,3-Benzothiazol-2-ylsulfanyl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3,5-dimethoxyphenyl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-methoxyphenyl)acetamide,

2-[5-Chloro-2-oxo-1,3-benzothiazol-3(2H)-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]acetamide,

2-(1-Benzothiophen-3-yl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(3,4-dimethoxyphenyl)butanamide,

5-Cyclohexyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]pentanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-fluoro-2-methylbenzamide,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(1-phenylethyl)phthalamide,

2-Cyclopentyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

4-Chloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-nitrobenzamide,

2,2-Dichloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1-methylcyclopropanecarboxamide,

tert-Butyl 4-[5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}carbonyl)-2-methoxyphenyl]-1-piperazinecarboxylate,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-1-(2-thienylmethyl)-3-pyrrolidinecarboxamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[2-oxo-1,3-benzoxazol-3(2H)-yl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-fluorobenzamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-methylbenzamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-methylbenzamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(hydroxymethyl)benzamide,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-{2-[(methylsulfanyl)methyl]-4-pyrimidinyl}-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[5-methoxy-2-(methylsulfanyl)-4-pyrimidinyl]-1,2-ethanediamine,

2-({4-[(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)amino]-2-pyrimidinyl}amino)-1-ethanol,

N~4~-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-6-methyl-2,4-pyrimidinediamine,

N~4~-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N~2~,6-dimethyl-2,4-pyrimidinediamine,

2-Chloro-N~4~-cyclopropyl-N~6~-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-4,6-pyrimidinediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(4-phenyl-2-pyrimidinyl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(trifluoromethyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(propylsulfanyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~2~-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N~4~,6-dimethyl-2,4-pyrimidinediamine,

N~4~-Cyclopropyl-N~2~-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-2,4-pyrimidinediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(3-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(3-thienyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(2-thienyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(1H-purin-6-yl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(5-methylthieno[2,3-d]pyrimidin-4-yl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(7-methylthieno[3,2-d]pyrimidin-4-yl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(9-methyl-9H-purin-6-yl)-1,2-ethanediamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-{[5-(trifluoromethyl)-2-pyridinyl]sulfanyl}acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-5-phenylpentanamide,

2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(phenylsulfanyl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine,

2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}-N-(3-methoxyphenyl)acetamide, dihydrochloride salt,

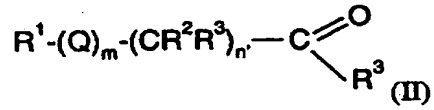
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3,4-dichlorophenyl)urea,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3-methoxyphenyl)urea, and

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methoxybenzyl)amine, dihydrochloride salt.

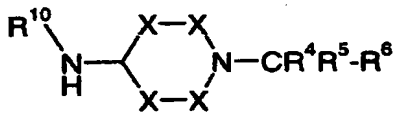
The present invention further provides a process for the preparation of a compound of formula (I) which comprises:

(a) when n is at least 1, the CR^2R^3 group attached directly to T is CHR^3 and T is NR^{10}, reacting a compound of general formula



(II)

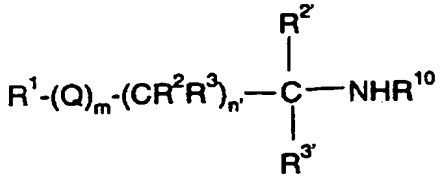
wherein n' is 0 or an integer from 1 to 3 and R^1, R^2, R^3, m and Q are as defined in formula (I), with a compound of general formula



(III)

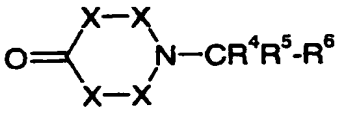
or a salt thereof, wherein X, R^4, R^5, R^6 and R^{10} are as defined in formula (I), in the presence of a reducing agent; or

(b) when n is at least 1, the CR^2R^3 group attached directly to T is $C(C_1\text{-}C_4\ alkyl)_2$ and T is NR^{10}, reacting a compound of general formula



(IV)

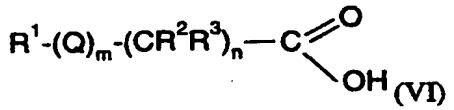
wherein n' is 0 or an integer from 1 to 3, $R^{2'}$ and $R^{3'}$ each independently represent a C_1-C_4 alkyl group, and R^1, R^2, R^3, R^{10}, m and Q are as defined in formula (I), with a compound of general formula



(V)

wherein X, R^4, R^5 and R^6 are as defined in formula (I), in the presence of a reducing agent; or

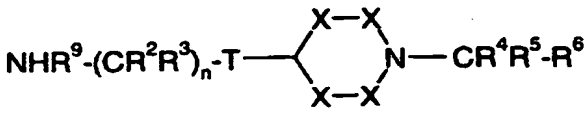
(c) when T is $C(O)NR^{10}$, reacting a compound of general formula



(VI)

wherein R^1, R^2, R^3, Q, m and n are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

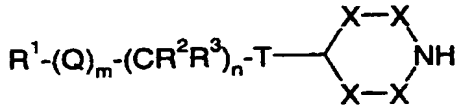
(d) when m is 1 and Q is NR^9, reacting a compound of general formula (VII), R^1 - L^1, wherein L^1 represents a leaving group (e.g. a halogen atom) and R^1 is as defined in formula (I), with a compound of general formula



(VIII)

or a salt thereof, wherein n, T, X, R^2, R^3, R^4, R^5, R^6 and R^9 are as defined in formula (I); or

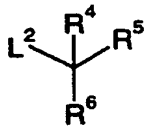
(e) when at least one of R^4 and R^5 represents a hydrogen atom, reacting a compound of general formula



(IX)

or a salt thereof, wherein R^1, R^2, R^3, Q, m, n, X and T are as defined in formula (I), with a compound of general formula (X), R^6 - C(O) - R^{20}, wherein R^{20} represents a hydrogen atom or a C_1-C_4 alkyl group and R^6 is as defined in formula (I), in the presence of a reducing agent; or

(f) reacting a compound of formula (IX) as defined in (e) above, with a compound of general formula



(XI)

wherein L^2 represents a leaving group (e.g. a halogen atom) and R^4, R^5 and R^6 are as defined in formula (I); or

(g) when T is NR^{10}, reacting a compound of general formula

(XII)

wherein L^3 represents a leaving group (e.g. a halogen atom) and R^1, R^2, R^3, m, n and Q are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

(h) when T is $NHC(O)NR^{10}$, reacting a compound of general formula

$$R^1\text{-}(Q)_m\text{-}(CR^2R^3)_n\text{—}\ N{=}C{=}O \quad \text{(XIII)}$$

wherein R^1, R^2, R^3, Q, m and n are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above;

and optionally after (a), (b), (c), (d), (e), (f), (g) or (h) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained.

Compounds of formulae (II) to (XIII) are either commercially available, or are known in the literature or may be prepared using known techniques.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of the invention and intermediates may be isolated from their reaction mixtures, and if necessary further purified, by using standard techniques.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor activity. More particularly, the compounds have utility as modulators of the activity of chemokine receptors CCR1 and/or CCR3.

A further aspect of the invention involves the use of a compound of general formula (I) in the treatment of conditions or diseases in which modulation of chemokine receptor activity is beneficial.

Thus, compounds of general formula (I) may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS). Examples of these conditions include:

(1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, osteoarthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus,

Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura; and

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The invention also provides a method of treating an inflammatory disease in a person suffering from, or at risk of, said disease, which comprises administering to the person a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

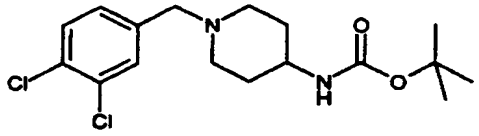
The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will be further explained by reference to the following illustrative examples.

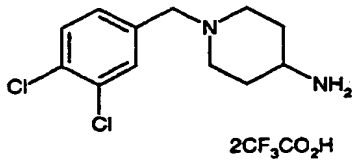
Examples 1-47

(i) tert-Butyl 1-(3,4-dichlorobenzyl)-4-piperidinylcarbamate



Sodium triacetoxyborohydride (6g) was added to a stirred solution of 3,4-dichlorobenzaldehyde (4.2g) and 1,1-dimethylethyl-4-piperidinyl carbamate (4g) in dichloromethane (50ml). The mixture was stirred at room temperature for 4h then partitioned between ethyl acetate and aqueous sodium hydrogencarbonate. The organic layer was washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether to give a white solid (3.5g). Used directly.

(ii) 1-(3,4-Dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt



The product from step (i) (3.5g) was treated with trifluoroacetic acid (10ml) in dichloromethane (40ml). After 72h, the solution was evaporated, the residue triturated with ether and the solid (4.3g) collected.

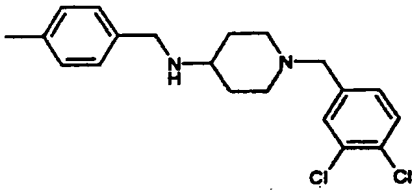
MS: APCI(+ve) 259/61 (M+1)

(iii) Examples 1-47

The product from step (ii) (2mg), the appropriate aldehyde (2 equivalents), sodium triacetoxyborohydride (3 equivalents) and diisopropylethylamine (2 equivalents) in acetonitrile (0.08ml) and 1-methyl-2-pyrrolidinone (0.12ml) was left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsuphoxide (0.4ml).

Example 1

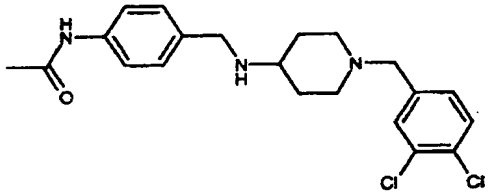
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methylbenzyl)amine



MS: APCI(+ve) 363 (M+1)

Example 2

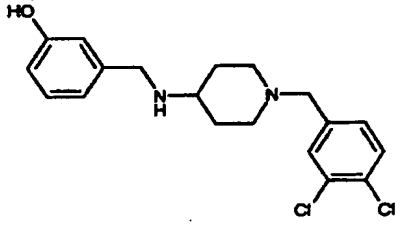
N-[4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenyl]acetamide



MS: APCI(+ve) 406 (M+1)

Example 3

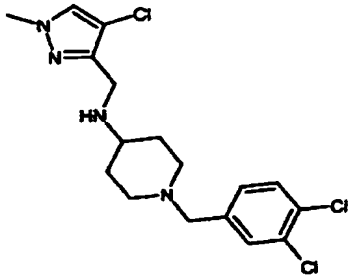
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenol



MS: APCI(+ve) 365 (M+1)

Example 4

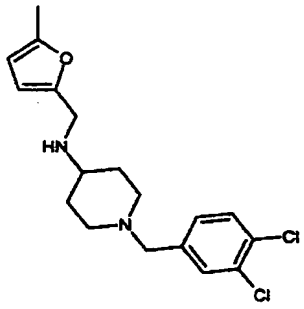
N-[(4-Chloro-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 389 (M+1)

Example 5

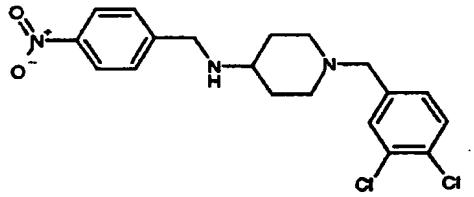
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-furyl)methyl]amine



MS: APCI(+ve) 353 (M+1)

Example 6

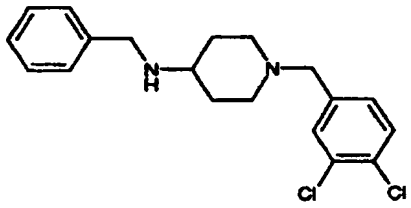
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-nitrobenzyl)amine



MS: APCI(+ve) 394 (M+1)

Example 7

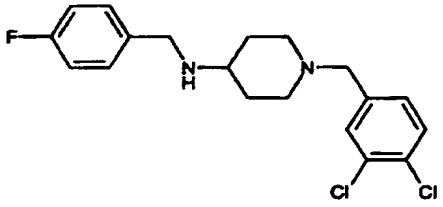
N-Benzyl-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 349 (M+1)

Example 8

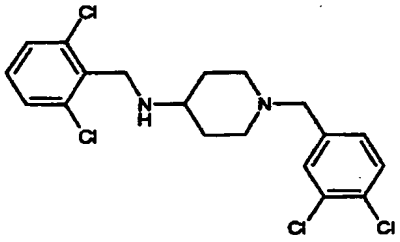
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-fluorobenzyl)amine



MS: APCI(+ve) 367 (M+1)

Example 9

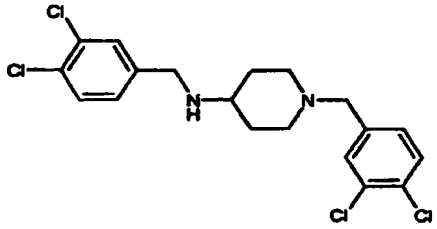
N-(2,6-Dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 419 (M+1)

Example 10

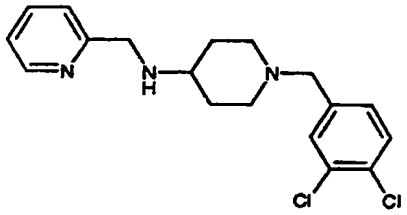
N,1-Bis(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 419 (M+1)

Example 11

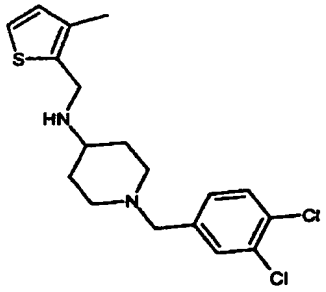
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-pyridinylmethyl)amine



MS: APCI(+ve) 350 (M+1)

Example 12

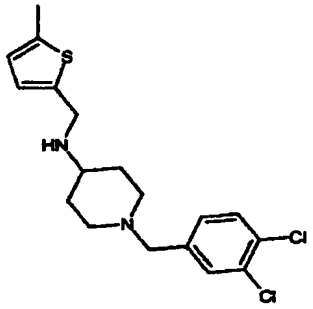
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(3-methyl-2-thienyl)methyl]amine



MS: APCI(+ve) 369 (M+1)

Example 13

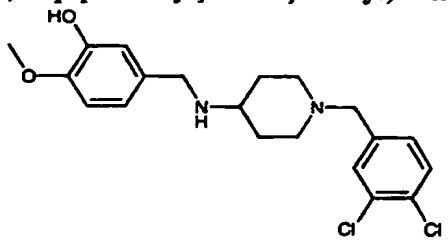
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-thienyl)methyl]amine



MS: APCI(+ve) 369 (M+1)

Example 14

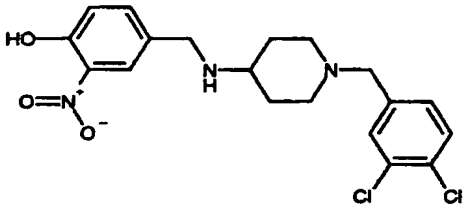
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methoxyphenol



MS: APCI(+ve) 395 (M+1)

Example 15

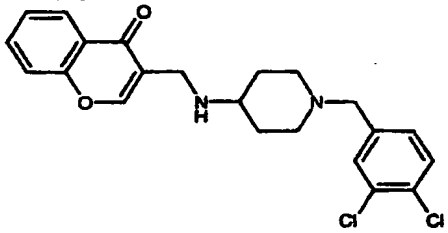
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol



MS: APCI(+ve) 410 (M+1)

Example 16

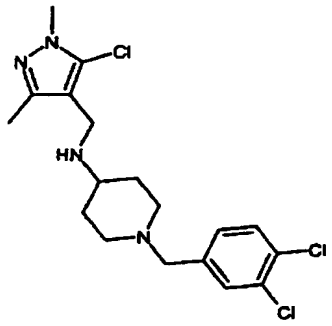
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-4H-chromen-4-one



MS: APCI(+ve) 417 (M+1)

Example 17

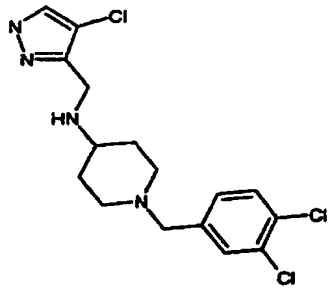
N-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 403 (M+1)

Example 18

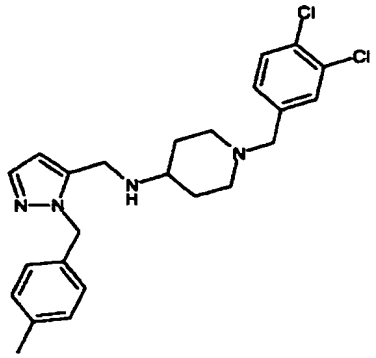
N-[(4-Chloro-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 373 (M+1)

Example 19

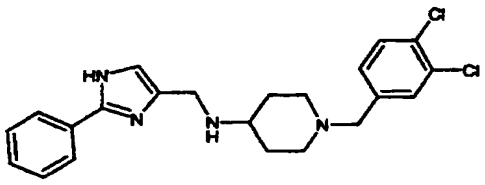
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-{[1-(4-methylbenzyl)-1H-pyrazol-5-yl]methyl}amine



MS: APCI(+ve) 443 (M+1)

Example 20

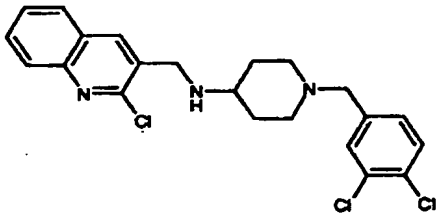
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(2-phenyl-1H-imidazol-4-yl)methyl]amine



MS: APCI(+ve) 414 (M+1)

Example 21

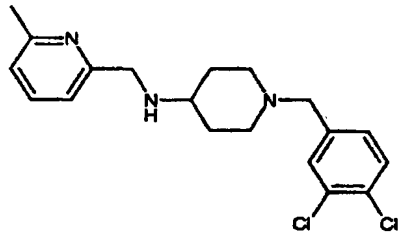
N-[(2-Chloro-3-quinolinyl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 434 (M+1)

Example 22

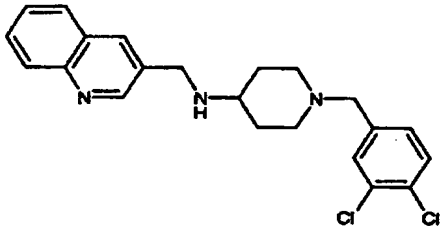
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(6-methyl-2-pyridinyl)methyl]amine



MS: APCI(+ve) 364 (M+1)

Example 23

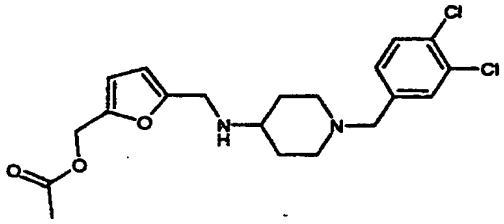
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-quinolinylmethyl)amine



MS: APCI(+ve) 400 (M+1)

Example 24

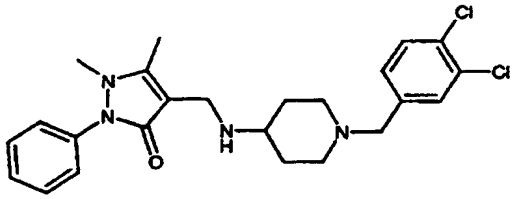
[5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-furyl]methyl acetate



MS: APCI(+ve) 411 (M+1)

Example 25

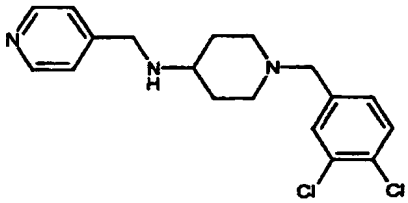
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one



MS: APCI(+ve) 459 (M+1)

Example 26

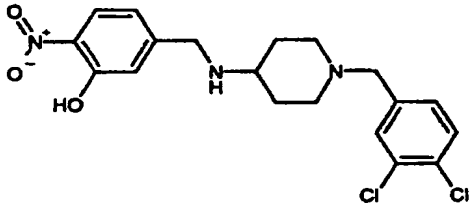
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-pyridinylmethyl)amine



MS: APCI(+ve) 350 (M+1)

Example 27

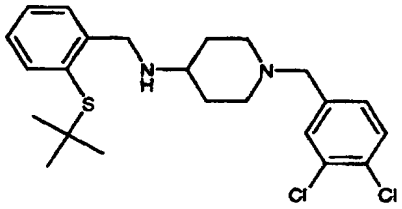
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol



MS: APCI(+ve) 410 (M+1)

Example 28

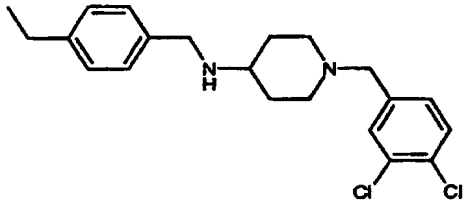
N-[2-(tert-Butylsulfanyl)benzyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 437 (M+1)

Example 29

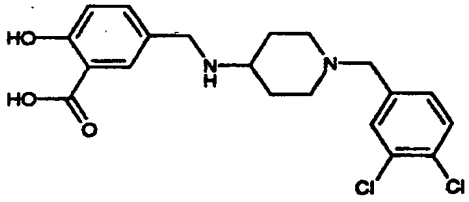
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-ethylbenzyl)amine



MS: APCI(+ve) 377 (M+1)

Example 30

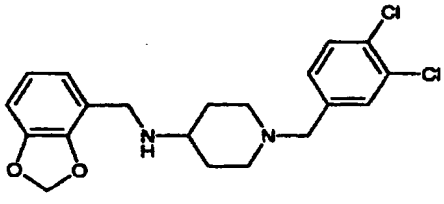
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxybenzoic acid



MS: APCI(+ve) 409 (M+1)

Example 31

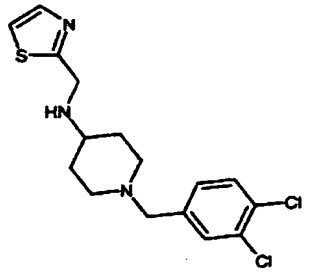
N-(1,3-Benzodioxol-4-ylmethyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 393 (M+1)

Example 32

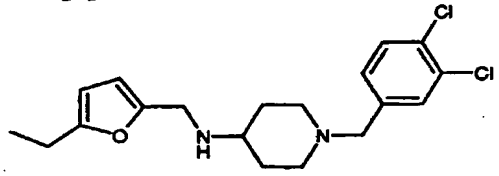
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(1,3-thiazol-2-ylmethyl)amine



MS: APCI(+ve) 356 (M+1)

Example 33

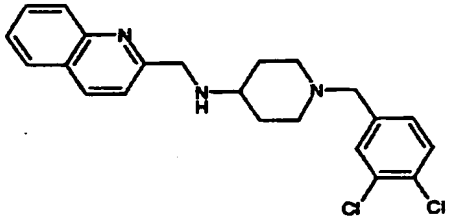
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-ethyl-2-furyl)methyl]amine



MS: APCI(+ve) 367 (M+1)

Example 34

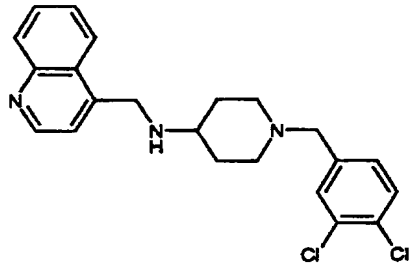
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-quinolinylmethyl)amine



MS: APCI(+ve) 400 (M+1)

Example 35

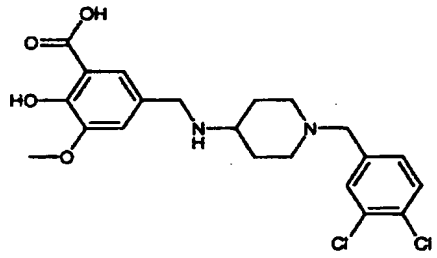
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-quinolinylmethyl)amine



MS: APCI(+ve) 400 (M+1)

Example 36

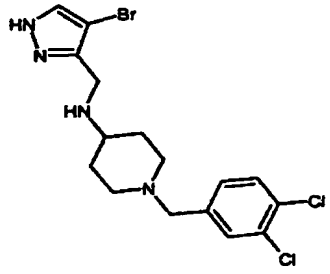
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxy-3-methoxybenzoic acid



MS: APCI(+ve) 439 (M+1)

Example 37

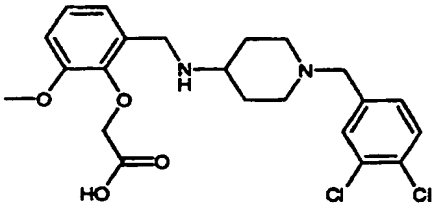
N-[(4-Bromo-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 419 (M+1)

Example 38

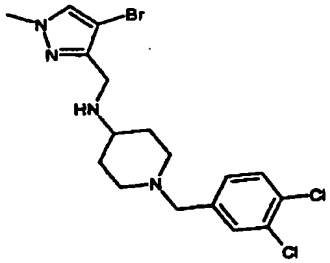
2-[2-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6-methoxyphenoxy]acetic acid



MS: APCI(+ve) 453 (M+1)

Example 39

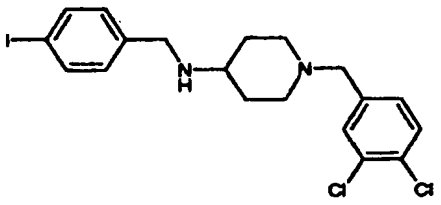
N-[(4-Bromo-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



MS: APCI(+ve) 433 (M+1)

Example 40

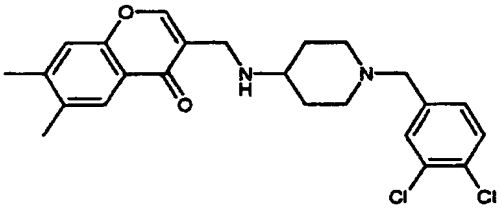
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-iodobenzyl)amine



MS: APCI(+ve) 475 (M+1)

Example 41

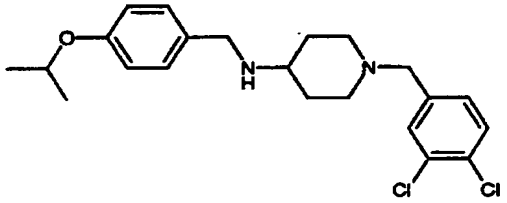
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6,7-dimethyl-4H-chromen-4-one



MS: APCI(+ve) 445 (M+1)

Example 42

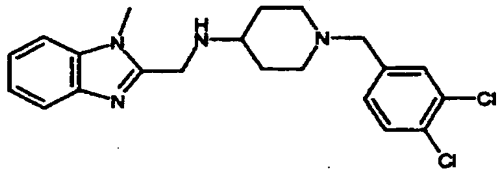
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-isopropoxybenzyl)amine



MS: APCI(+ve) 407 (M+1)

Example 43

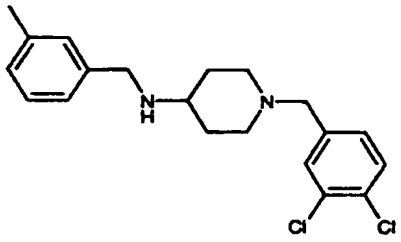
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]amine



MS: APCI(+ve) 403 (M+1)

Example 44

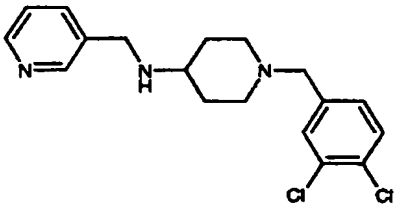
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-methylbenzyl)amine



MS: APCI(+ve) 363 (M+1)

Example 45

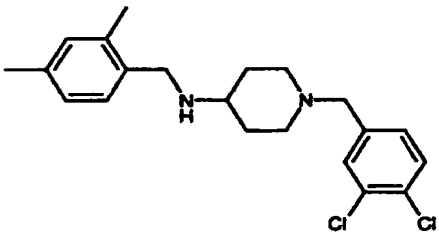
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-pyridinylmethyl)amine



MS: APCI(+ve) 350 (M+1)

Example 46

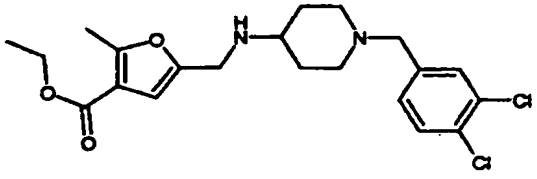
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2,4-dimethylbenzyl)amine



MS: APCI(+ve) 377 (M+1)

Example 47

Ethyl 5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methyl-3-furoate



MS: APCI(+ve) 425 (M+1)

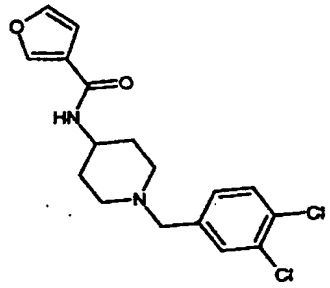
Examples 48-73

(i) Examples 48-73

Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (2 equiv) was added to a solution of the product from Example 1 step (ii) (hydrochloride salt) (1mg), the appropriate acid (2 equivalents) and diisopropylethylamine (5 equivalents) in dimethylformamide (0.17ml) and was left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.3ml).

Example 48

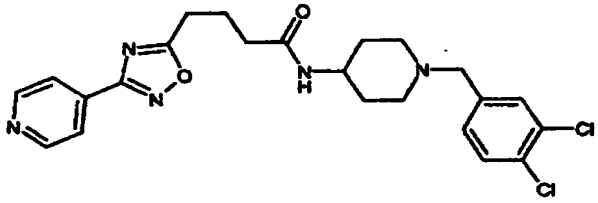
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-furamide



MS: APCI(+ve) 353 (M+1)

Example 49

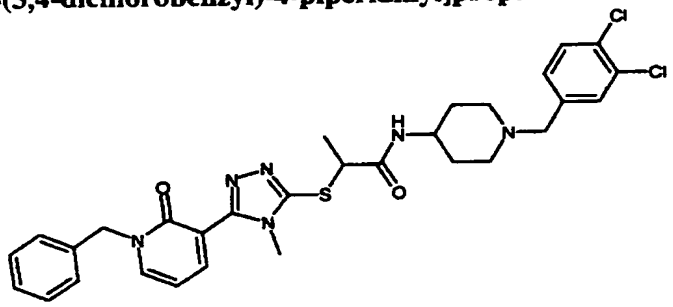
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]butanamide



MS: APCI(+ve) 474 (M+1)

Exampl 50

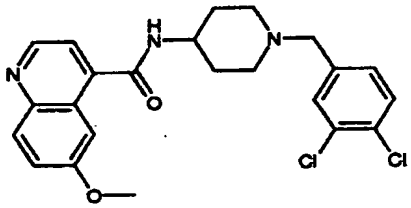
2-{[5-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide



MS: APCI(+ve) 611 (M+1)

Example 51

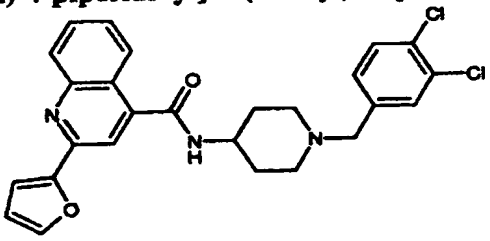
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-6-methoxy-4-quinolinecarboxamide



MS: APCI(+ve) 444 (M+1)

Example 52

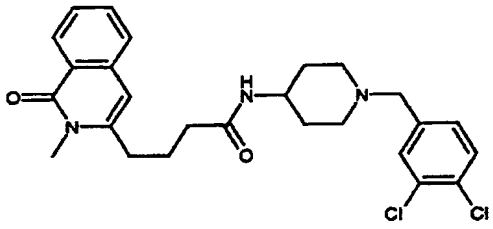
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-furyl)-4-quinolinecarboxamide



MS: APCI(+ve) 480 (M+1)

Example 53

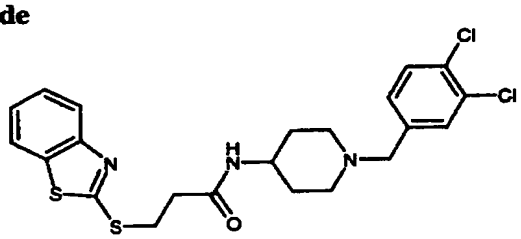
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butanamide



MS: APCI(+ve) 486 (M+1)

Example 54

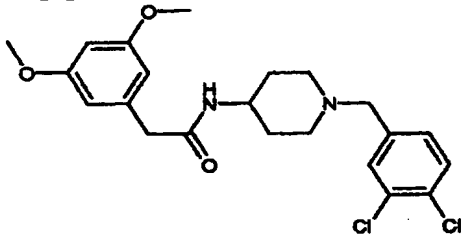
3-(1,3-Benzothiazol-2-ylsulfanyl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide



MS: APCI(+ve) 480 (M+1)

Example 55

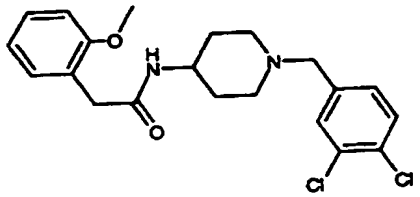
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3,5-dimethoxyphenyl)acetamide



MS: APCI(+ve) 437 (M+1)

Example 56

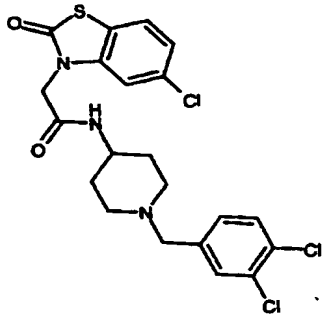
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-methoxyphenyl)acetamide



MS: APCI(+ve) 407 (M+1)

Example 57

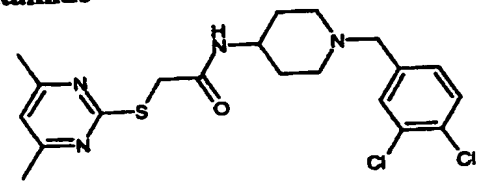
2-[5-Chloro-2-oxo-1,3-benzothiazol-3(2H)-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



MS: APCI(+ve) 486 (M+1)

Example 58

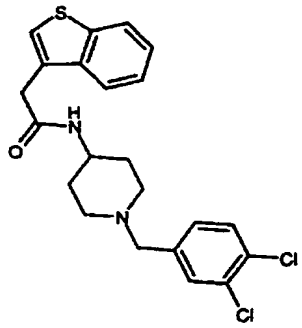
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]acetamide



MS: APCI(+ve) 439 (M+1)

Example 59

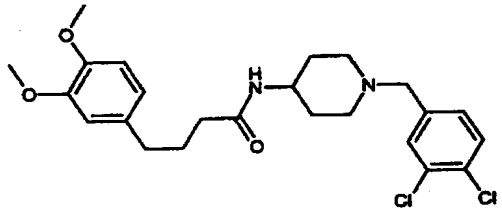
2-(1-Benzothiophen-3-yl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



MS: APCI(+ve) 433 (M+1)

Example 60

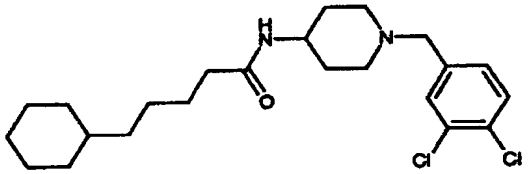
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(3,4-dimethoxyphenyl)butanamide



MS: APCI(+ve) 465 (M+1)

Example 61

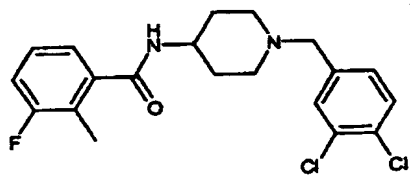
5-Cyclohexyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]pentanamide



MS: APCI(+ve) 425 (M+1)

Example 62

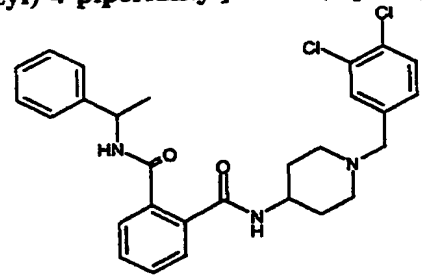
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-fluoro-2-methylbenzamide



MS: APCI(+ve) 395 (M+1)

Example 63

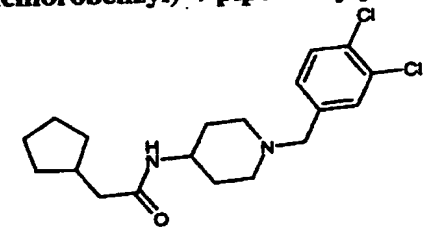
N~1~~[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~~(1-phenylethyl)phthalamide



MS: APCI(+ve) 510 (M+1)

Example 64

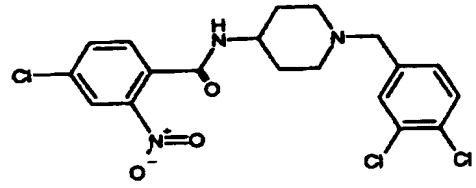
2-Cyclopentyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



MS: APCI(+ve) 369 (M+1)

Example 65

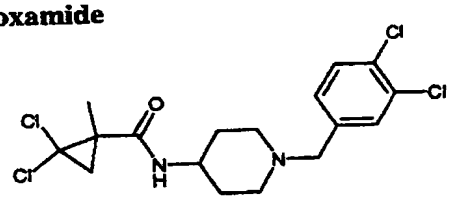
4-Chloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-nitrobenzamide



MS: APCI(+ve) 444 (M+1)

Example 66

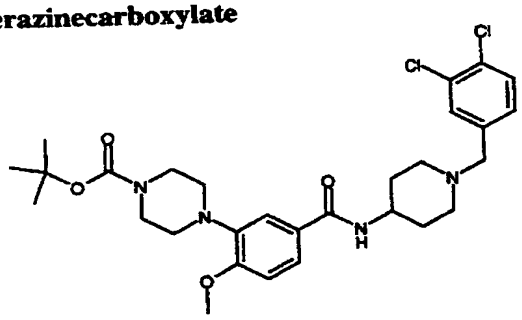
2,2-Dichloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1-methylcyclopropanecarboxamide



MS: APCI(+ve) 411 (M+1)

Example 67

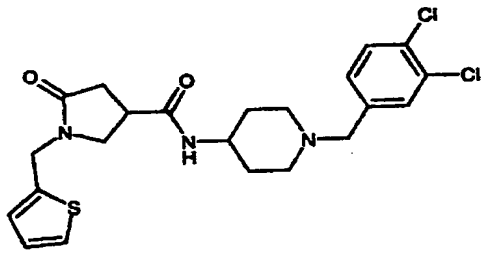
tert-Butyl 4-[5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}carbonyl)-2-methoxyphenyl]-1-piperazinecarboxylate



MS: APCI(+ve) 577 (M+1)

Example 68

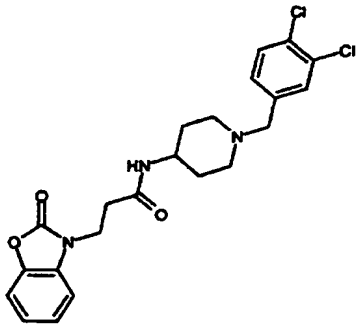
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-1-(2-thienylmethyl)-3-pyrrolidinecarboxamide



MS: APCI(+ve) 466 (M+1)

Example 69

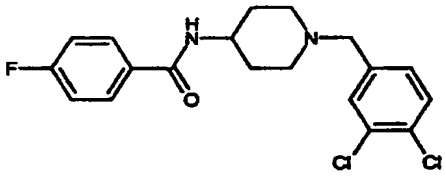
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[2-oxo-1,3-benzoxazol-3(2H)-yl]propanamide



MS: APCI(+ve) 448 (M+1)

Example 70

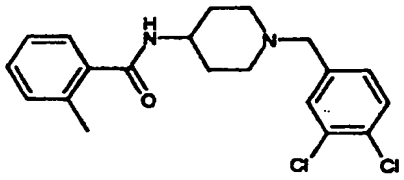
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-fluorobenzamide



MS: APCI(+ve) 381 (M+1)

Example 71

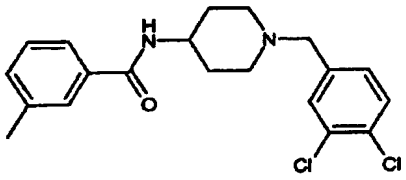
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-methylbenzamide



MS: APCI(+ve) 377 (M+1)

Example 72

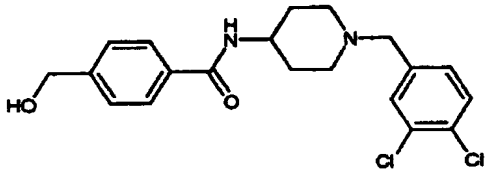
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-methylbenzamide



MS: APCI(+ve) 377 (M+1)

Example 73

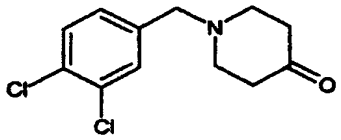
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(hydroxymethyl)benzamide



MS: APCI(+ve) 393 (M+1)

Examples 74-93

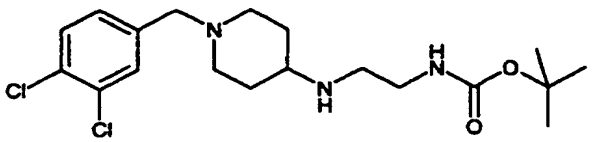
(i) 1-(3,4-Dichlorobenzyl)-4-piperidinone



A solution of 3,4-dichlorobenzyl chloride (2.8ml), 4-ketopiperidine hydrochloride monohydrate and triethylamine (8ml) in dimethylformamide (30ml) was stirred at room temperature for 20h. The mixture was partitioned between water and ethyl acetate, the organic layer dried and evaporated under reduced pressure. Purification was by chromatography eluting with 40-50% ethyl acetate/isohexane. Yield 2.1g.

MS: APCI(+ve) 258/60 (M+1)

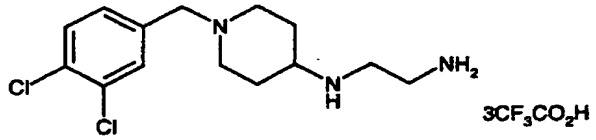
(ii) tert-Butyl 2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethylcarbamate



A solution of the product from step (i) (1.61g), N-(tert-butoxycarbonyl)-ethylenediamine (1g) and sodium triacetoxyborohydride (2.12g) in dichloromethane (20ml) was stirred at room temperature for 3h. The mixture was partitioned between water and ethyl acetate, the organic layer dried and evaporated under reduced pressure. Yield 1.28g.

MS: APCI(+ve) 402/4 (M+1)

(iii) N-1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1,2-ethanediamine, tri-trifluoroacetate salt



The product from step (ii) (1.28g) was treated with trifluoroacetic acid (5ml) in dichloromethane (10ml). After 20h, the solution was evaporated, the residue triturated with ether and the solid (1.62g) collected.

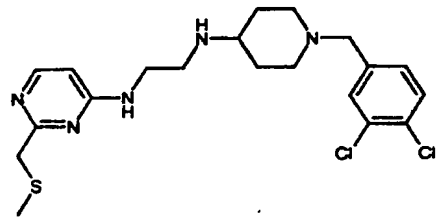
MS: APCI(+ve) 302/4 (M+1)

(iv) Examples 74-93

The product from step (iii) (0.0026g), the appropriate activated halo-aromatic (1.25 equivalents) and diisopropylethylamine (10 equivalents) in 1-methyl-2-pyrolidinone (0.15ml) was heated at 100°C for 20h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsuphoxide (0.4ml).

Example 74

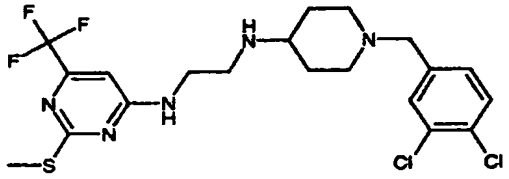
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--{2-[(methylsulfanyl)methyl]-4-pyrimidinyl}-1,2-ethanediamine



MS: APCI(+ve) 440(M+1)

Example 75

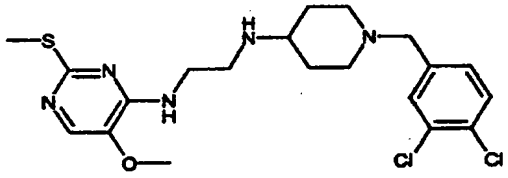
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--[2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 494(M+1)

Example 76

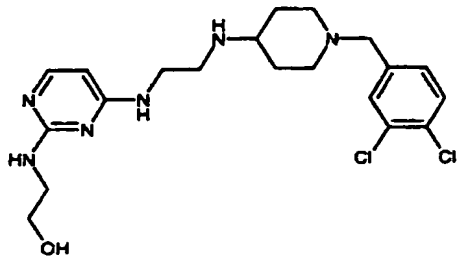
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--[5-methoxy-2-(methylsulfanyl)-4-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 456(M+1)

Example 77

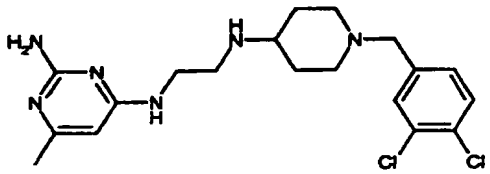
2-({4-[(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)amino]-2-pyrimidinyl}amino)-1-ethanol



MS: APCI(+ve) 439(M+1)

Example 78

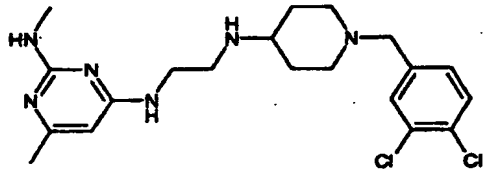
N~4~-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-6-methyl-2,4-pyrimidinediamine



MS: APCI(+ve) 409(M+1)

Example 79

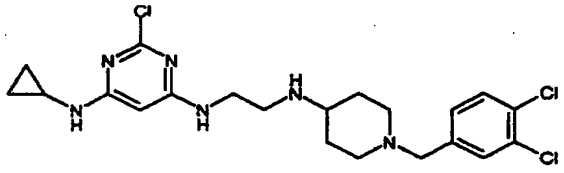
N~4~-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N~2~,6-dimethyl-2,4-pyrimidinediamine



MS: APCI(+ve) 423(M+1)

Example 80

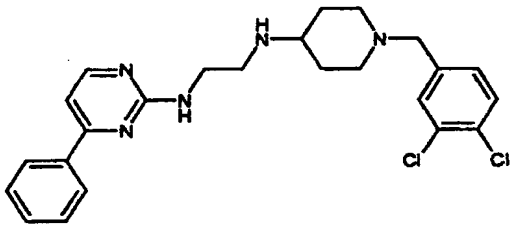
2-Chloro-N~4~-cyclopropyl-N~6~-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-4,6-pyrimidinediamine



MS: APCI(+ve) 471(M+1)

Example 81

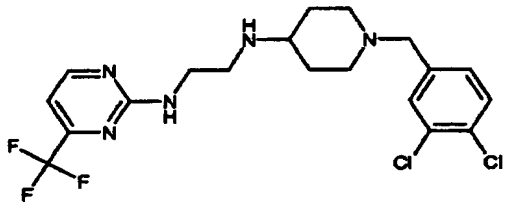
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--(4-phenyl-2-pyrimidinyl)-1,2-ethanediamine



MS: APCI(+ve) 456(M+1)

Example 82

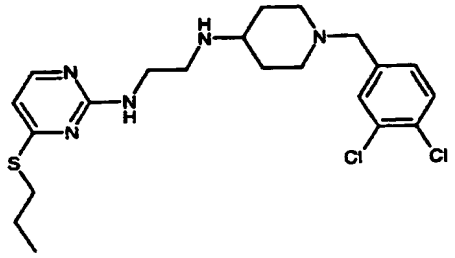
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--[4-(trifluoromethyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 448(M+1)

Example 83

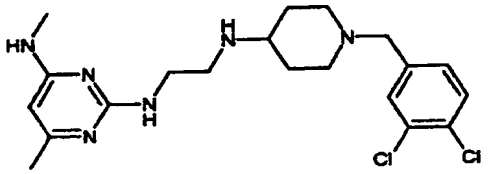
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--[4-(propylsulfanyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 454(M+1)

Example 84

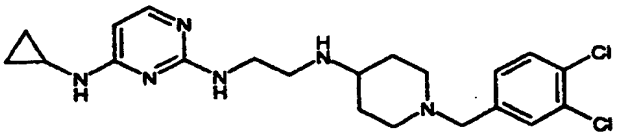
N~2~-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N~4~,6-dimethyl-2,4-pyrimidinediamine



MS: APCI(+ve) 423(M+1)

Example 85

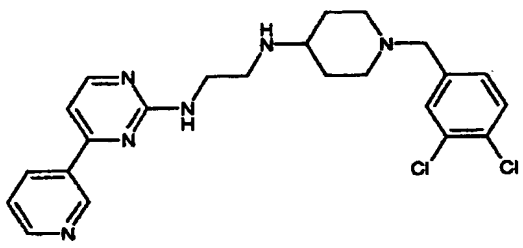
N~4~-Cyclopropyl-N~2~-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-2,4-pyrimidinediamine



MS: APCI(+ve) 435(M+1)

Example 86

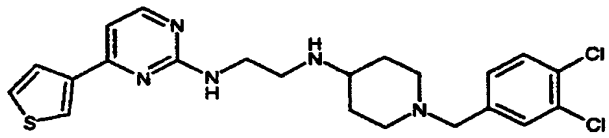
N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(3-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 457(M+1)

Example 87

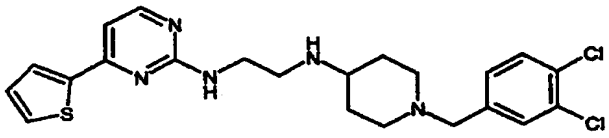
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--[4-(3-thienyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 462(M+1)

Example 88

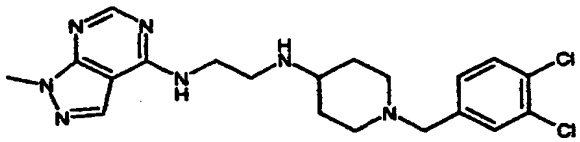
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--[4-(2-thienyl)-2-pyrimidinyl]-1,2-ethanediamine



MS: APCI(+ve) 462(M+1)

Example 89

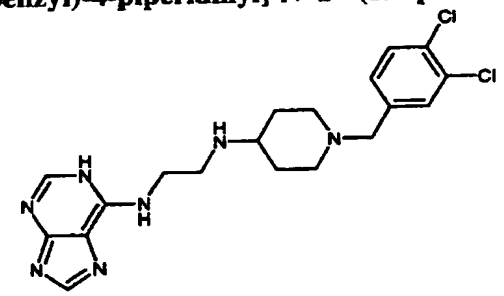
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--(1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-ethanediamine



MS: APCI(+ve) 434(M+1)

Example 90

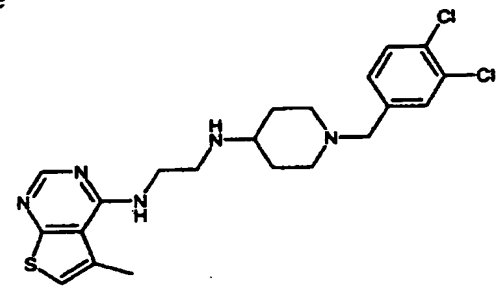
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--(1H-purin-6-yl)-1,2-ethanediamine



MS: APCI(+ve) 420(M+1)

Example 91

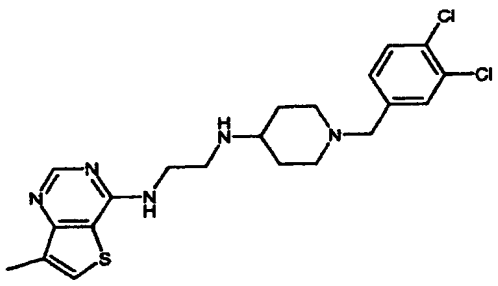
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--(5-methylthieno[2,3-d]pyrimidin-4-yl)-1,2-ethanediamine



MS: APCI(+ve) 450(M+1)

Example 92

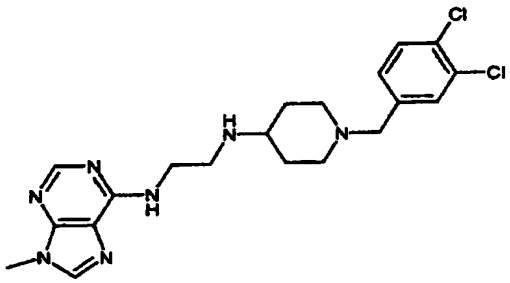
N~1~--[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~--(7-methylthieno[3,2-d]pyrimidin-4-yl)-1,2-ethanediamine



MS: APCI(+ve) 450(M+1)

Example 93

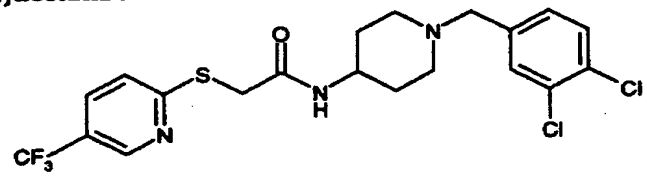
N~1~~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~~-(9-methyl-9H-purin-6-yl)-1,2-ethanediamine



MS: APCI(+ve) 434(M+1)

Example 94

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-{[5-(trifluoromethyl)-2-pyridinyl]sulfanyl}acetamide



Carbonyldiimidazole (0.105g) was added to a stirred solution of 2-{[5-(trifluoromethyl)-2-pyridinyl]sulfanyl}acetic acid (0.166g) in dimethylformamide (2ml). After 1h a solution of the product from Example 1 step (ii) (0.3g) in a solution of dimethylformamide and diisopropylethylamine (2 equivalents) (1.5ml) was added and stirred at room temperature for 2h. The mixture was partitioned between water and ethyl acetate, the organic layer

washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether and collected. Yield 0.084g as a solid.

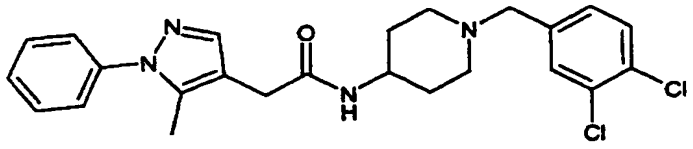
MS: APCI(+ve) 478/80 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.76(s, 1H), 8.11(d, 1H), 8.02(dd, 1H), 7.59-7.53(m, 3H), 7.29(dd, 1H), 3.91(s, 1H), 3.58-3.45(m, 1H), 3.44(s, 2H), 2.70(br d, 2H), 2.03(br t, 2H), 1.70(br d, 2H), 1.46-1.37(m, 2H).

MP: 98°C

Example 95

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and of 2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetic acid (0.151g) using the method of Example 94. Yield 0.18g as a solid.

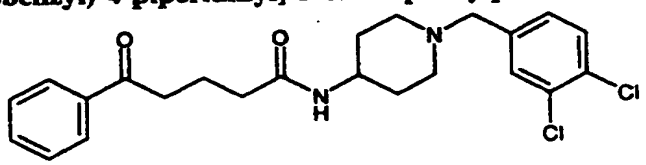
MS: APCI(+ve) 457/9 (M+1)

^{1}H NMR: δ (DMSO-d6) 7.90(d, 1H), 7.59-7.38(m, 8H), 7.29(dd, 1H), 3.54-3.50(m, 1H), 3.45(s, 2H), 3.24(s, 2H), 2.72(br d, 2H), 2.24(s, 3H), 2.03(br t, 2H), 1.72(br d, 2H), 1.46-1.37(m, 2H).

MP: 165°C

Example 96

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-5-phenylpentanamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and of 5-oxo-5-phenylpentanoic acid (0.134g) using the method of Example 94. Yield 0.149g as a solid.

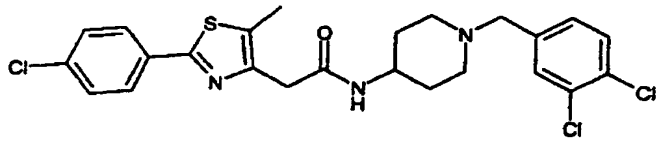
MS: APCI(+ve) 433/5 (M+1)

^{1}H NMR: δ (DMSO-d6) 7.96-7.93(m, 2H), 7.72(d, 1H), 7.65-7.50(m, 5H), 7.28(dd, 1H), 3.57-3.48(m, 1H), 3.44(s, 2H), 3.01(t, 2H), 2.72-2.67(m, 2H), 2.13(t, 2H), 2.04-1.98(m, 2H), 1.86-1.79(m, 2H), 1.69(br s, 2H), 1.41-1.32(m, 2H).

MP: 130°C

Example 97

2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-[2-(4-chlorophenyl)-5-methyl-1,3-thiazol-4-yl]acetic acid (0.187g) using the method of Example 94. Yield 0.1g as a solid.

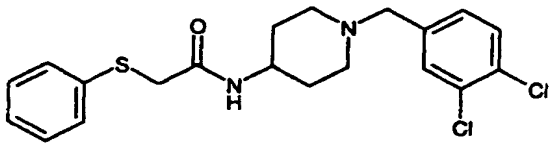
MS: APCI(+ve) 510/2 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.00(d, 1H), 7.85-7.82(m, 2H), 7.59-7.52(m, 4H), 7.29(dd, 1H), 3.57-3.51(m, 3H), 3.44(s, 2H), 2.72(br d, 2H), 2.41(s, 3H), 2.06(t, 2H), 1.73(br d, 2H), 1.48-1.38(m, 2H).

MP: 170°C

Example 98

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(phenylsulfanyl)acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-(phenylsulfanyl)acetic acid (0.118g) using the method of Example 94. Yield 0.056g as a solid.

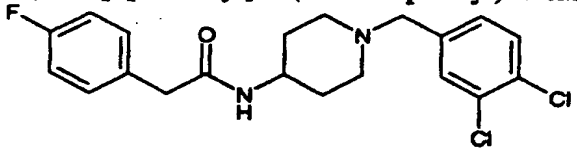
MS: APCI(+ve) 409 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.00(d, 1H), 7.57(d, 1H), 7.53(d, 1H), 7.36-7.27(m, 5H), 7.20-7.16(m, 1H), 3.61(s, 2H), 3.55-3.47(m, 1H), 3.44(s, 2H), 2.69-2.66(m, 2H), 2.02(t, 2H), 1.67-1.64(m, 2H), 1.41-1.31(m, 2H).

MP: 97-99°C

Example 99

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-(4-fluorophenyl)acetic acid (0.108g) using the method of Example 94. Yield 0.15g as a solid.

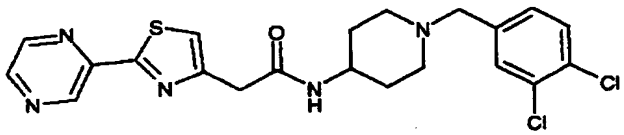
MS: APCI(+ve) 395 (M+1)

^{1}H NMR: δ (DMSO-d6) 7.98(d, 1H), 7.57(d, 1H), 7.53(d, 1H), 7.30-7.25(m, 3H), 7.13-7.07(m, 2H), 3.54-3.48(m, 1H), 3.45(s, 2H), 3.37(s, 2H), 2.72-2.69(m, 2H), 2.02(t, 2H), 1.71-1.68(m, 2H), 1.44-1.34(m, 2H).

MP: 144-7°C

Example 100

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetic acid (0.155g) using the method of Example 94. Yield 0.08g as a solid.

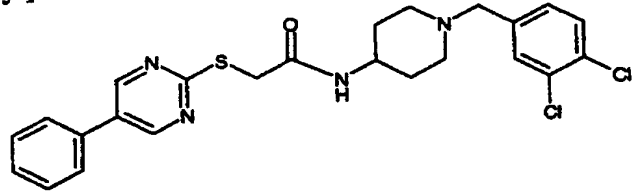
MS: APCI(+ve) 462 (M+1)

^{1}H NMR: δ (DMSO-d6) 9.25(d, 1H), 8.74-8.71(m, 2H), 8.07(d, 1H), 7.64(s, 1H), 7.59-7.54(m, 2H), 7.31-7.28(m, 1H), 3.69(s, 2H), 3.59-3.54(m, 1H), 3.45(s, 2H), 2.74-2.71(m, 2H), 2.04(t, 2H), 1.76-1.74(m, 2H), 1.49-1.39(m, 2H).

MP: 186-9°C

Example 101

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetamide



The title compound was prepared from the product of Example 1 step (ii) (0.3g) and 2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetic acid (0.172g) using the method of Example 94. Yield 0.115g as a solid.

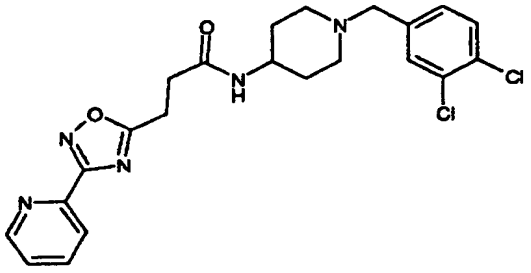
MS: APCI(+ve) 487/9 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.96(s, 2H), 8.09(d, 1H), 7.78-7.75(m, 2H), 7.58-7.43(m, 5H), 7.28(dd, 1H), 3.91(s, 2H), 3.59-3.52(m, 1H), 3.44(s, 2H), 2.70(br d, 2H), 2.03(br t, 2H), 1.72(br d, 2H), 1.47-1.38(m, 2H).

MP: 157°C

Example 102

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide



The title compound was prepared from the product of Example 1 step (ii) (0.9g) and 3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.3g) using the method of Example 94. Yield 0.074g as a solid.

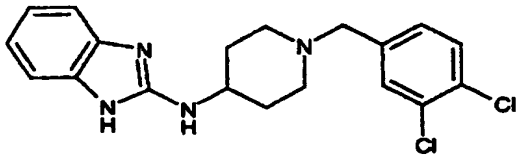
MS: APCI(+ve) 460/2 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.76-8.74(m, 1H), 8.05-7.99(m, 2H), 7.94(d, 1H), 7.61-7.56(m, 2H), 7.52(d, 1H), 7.28(dd, 1H), 3.56-3.48(m, 1H), 3.43(s, 2H), 3.19(t, 2H), 2.71-2.66(m, 4H), 2.03(t, 2H), 1.69(br d, 2H), 1.42-1.33(m, 2H).

MP: 155°C

Example 103

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine



(i) Ethyl 4-(1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate

A solution of 2-chlorobenzimidazole (1g) and ethyl 4-amino-1-piperidinecarboxylate (2g) in 1-methyl-2-pyrrolidinone was heated at 130°C for 24h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and

evaporated under reduced pressure. Purification was by chromatography eluting with 1% triethylamine/5% methanol in dichloromethane. Yield 0.630g as a solid.

TOF MS ES+ 289.1652 (M+1)

(ii) N-(4-Piperidinyl)-1H-benzimidazol-2-amine, dihydrochloride salt

The product from step (i) (0.58g) was heated under reflux with 5M hydrochloric acid (20ml) for 24h. The solvent was evaporated under reduced pressure, the residue azeotroped with toluene, washed with ether. Yield 0.58g as a solid.

TOF MS ES+ 217.1452 (M+1)

(iii) N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine

Triethylamine (0.223ml) was added to a stirred suspension of the product from step (ii) (0.2g) in dimethylformamide. After 5min 3,4-dichlorobenzaldehyde (0.175g) then sodium triacetoxyborohydride (0.212g) was added and the mixture stirred at room temperature for 3h. The mixture was partitioned between 2M hydrochloric acid and ether, the aqueous layer was basified with aqueous sodium hydrogencarbonate and extracted with ethyl acetate. The organic layer was dried and evaporated under reduced pressure. The residue was triturated with ethyl acetate/ether and the solid collected. Yield 0.045g.

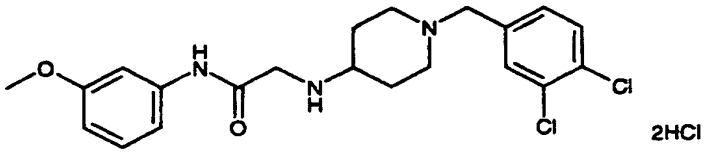
TOF MS ES+ 375.4257 (M+1)

^{1}H NMR: δ (DMSO-d6) 10.6(br s, 1H), 7.60-7.56(m, 2H), 7.32(dd, 1H), 7.12-7.09(m, 2H), 6.86-6.83(m, 2H), 6.49(d, 1H), 3.55-3.49(m, 3H), 2.79-2.71(m, 2H), 2.13-1.91(m, 4H), 1.56-1.46(m, 2H).

MP: 125°C

Example 104

2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}-N-(3-methoxyphenyl)acetamide, dihydrochloride salt



2-Chloro-N-(3-methoxyphenyl)-acetamide (0.241g) was added to a stirred solution of the product of Example 1 step (ii) (dihydrochloride salt) (0.4g), triethylamine (0.608g) in 1-methyl-2-pyrrolidinone (5ml). The reaction mixture was heated at 80°C for 6h then partitioned between ethyl acetate and brine. The organic layer was washed with brine, dried and evaporated under reduced pressure. Purification was by chromatography eluting with chloroform/isohexane/triethylamine/methanol 30:15:3:0.5. The resulting product was converted to the hydrochloride salt using ethereal hydrogenchloride. Yield 0.135g.

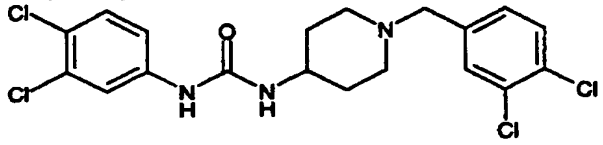
TOF MS ES+ 422.1406 (M+1)

^{1}H NMR: δ (DMSO-d6) 11.21(br s, 1H), 10.82(s, 1H), 9.53(br s, 2H), 7.95(s, 1H), 7.75(d, 1H), 7.60(d, 1H), 7.31-7.23(m, 2H), 7.15(d, 1H), 6.70(dd, 1H), 4.28(br s, 2H), 3.97(br , H), 3.73(s, 3H), 2.96(br, 2H), 2.28-2.05(m, 4H).

MP: 274-6°C

Example 105

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3,4-dichlorophenyl)urea



3,4-Dichlorophenyl isocyanate (0.081g) was added to a stirred solution of the product from Example 1 step (ii) (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure. Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid.

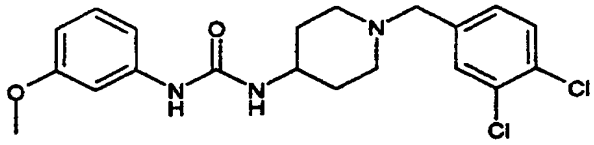
TOF MS ES+ 446.0360 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.65(s, 1H), 7.82(d, 1H), 7.59(d, 1H), 7.54(s, 1H), 7.31(d, 1H), 7.22(dd, 1H), 6.26(d, 1H), 3.45(br s , 3H), 2.67(m, 2H), 2.11(m, 2H), 1.81(m, 2H), 1.40(m, 2H).

MP: 189-190°C

Example 106

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3-methoxyphenyl)urea



3-Methoxyphenyl isocyanate (0.064g) was added to a stirred solution of the product from Example 1 step (ii) (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure. Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid.

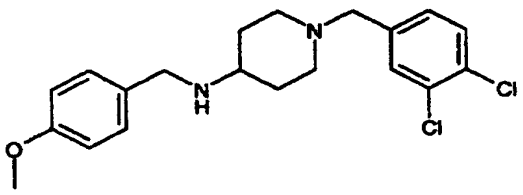
MS: APCI(+ve) 408/10 (M+1)

^{1}H NMR: δ (DMSO-d6) 8.32(s, 1H), 7.59(d, 1H), 7.55(d, 1H), 7.31(dd, 1H), 7.13(m, 1H), 7.09(d, 1H), 6.83(dd,1H), 6.47(dd, 1H), 6.09(d, 1H), 3.69(s, 3H), 3.46(m , 3H), 2.66(m, 2H), 2.13(m, 2H), 1.81(m, 2H), 1.42(m, 2H).

MP: 178-9°C

Example 107

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methoxybenzyl)amine, dihydrochloride salt



2HCl

The title compound was prepared from the product of Example 1 step (ii) (0.185g) and 4-methoxybenzaldehyde (0.49ul) using the method of Example 1 step (i). Yield 0.84g as a solid.

MS: APCI(+ve) 379/81 (M+1)

^{1}H NMR: δ (DMSO-d6) 11.33(br s, 1H), 9.56(br s, 2H), 7.96 (s, 1H), 7.74(d, 1H), 7.61(d, 1H), 7.52(d, 1H), 6.97(d, 1H), 4.27(s, 2H), 4.07(s,2H), 3.77(s, 3H), 3.39-2.94(m, 5H), 2.32-2.28(m, 2H), 2.15-2.07(m, 2H).

MP: >250°C

Pharmacological Analysis

Calcium flux [Ca^{2+}]$_i$ assay

a) Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5x10^6$ ml^{-1}) and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5μM fibronectin for two hours) at 100ml/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in dimethylsulphoxide and added to a final concentration of 0.1%(v/v) dimethylsulphoxide. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

b) Human monocytes

Human monocytes were isolated from EDTA anticoagulated peripheral blood as previously described (Cunoosamy & Holbrook, J. Leukocyte Biology, 1998, S2, 13). Cells were resuspended ($5x10^6$ ml^{-1}) in LKS and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $0.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPr plates (Costar). To each well 100μl of cells were added at a concentration of $0.5x10^6$ ml^{-1}. The plates were centrifuged (200g; 5 mins; room temperature) to allow the cells to adhere. After centrifugation the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in dimethylsulphoxide and added to a final concentration of 0.1%(v/v) dimethylsulphoxide. Assays were initiated by the addition of an A_{50} concentration of MIP-1α and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

The compounds of the Examples were found to be antagonists of the eotaxin mediated $[Ca^{2+}]_i$ in human eosinophils and/or antagonists of the MIP-1α mediated $[Ca^{2+}]_i$ in human monocytes.

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ ml^{-1} in RPMI containing 200 IU/ml penicillin, 200 μg/ml streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% dimethylsulphoxide). The

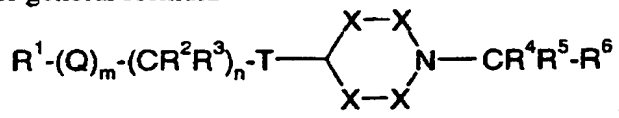
chemotaxis plate (ChemoTx, 3μm pore, Neuroprobe) was loaded by adding 28μl of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO_2 atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 μl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Certain compounds of the Examples were found to be antagonists of the eotaxin mediated human eosinophil chemotaxis.

CLAIMS

1. A compound of general formula

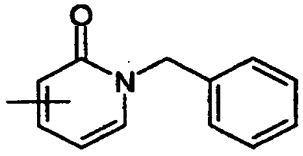


(I)

wherein

R^1 represents a C_1-C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio and C_1-C_6 alkoxycarbonyl, or

R^1 represents a 3- to 10-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from halogen, cyano, nitro, hydroxyl, carboxyl, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, carboxy-substituted C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylthiomethyl, C_1-C_6 alkylcarbonylamino, $-NR^7R^8$, $-C(O)NR^7R^8$, C_1-C_6 alkylcarbonyloxymethyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxycarbonylpiperazinyl, furyl, phenyl, pyridinyl, pyrazinyl, halophenyl, thienyl, thienylmethyl, C_1-C_6 alkylbenzyl and



;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR^9, C(O), $C(O)NR^9$ or $NR^9C(O)$;

n is 0, 1, 2, 3 or 4, provided that when n is 0, then m is 0;

each R^2 and R^3 independently represents a hydrogen atom or a C_1-C_4 alkyl group;

T represents a group NR^{10}, $C(O)NR^{10}$ or $NR^{11}C(O)NR^{10}$;

each X independently represents a group CH_2, CHR^{12} or C=O, provided that at least two groups X simultaneously represent CH_2;

R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_4 alkyl group;
R^6 represents a phenyl group optionally substituted by one or more substituents independently selected from halogen, amino ($-NH_2$), nitro, cyano, sulphonyl ($-SO_3H$), sulphonamido ($-SO_2NH_2$), C_1-C_6 alkyl, C_1-C_6 haloalkoxy and C_1-C_6 alkylsulphonyl;
R^7 and R^8 each independently represent a hydrogen atom or a group selected from C_1-C_6 hydroxyalkyl, C_3-C_6 cycloalkyl and C_1-C_6 alkyl optionally substituted by phenyl;
R^9, R^{10} and R^{11} each independently represent a hydrogen atom, or a C_1-C_4 alkyl or cyclopropylmethyl group; and
each R^{12} independently represents a C_1-C_4 alkyl or cyclopropylmethyl group;
or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein Q represents a sulphur atom or a group NH, C(O) or NHC(O).

3. A compound according to claim 1 or claim 2, wherein T represents a group NH, C(O)NH or NHC(O)NH.

4. A compound according to any one of claims 1 to 3, wherein all four groups X represent CH_2.

5. A compound according to claim 1 which is selected from:
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methylbenzyl)amine,
N-[4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenyl]acetamide,
3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenol,
N-[(4-Chloro-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-furyl)methyl]amine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-nitrobenzyl)amine,
N-Benzyl-1-(3,4-dichlorobenzyl)-4-piperidinamine,
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-fluorobenzyl)amine,
N-(2,6-Dichlor benzyl)-1-(3,4-dichl robenzyl)-4-piperidinamine,

N,1-Bis(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-pyridinylmethyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(3-methyl-2-thienyl)methyl]amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-thienyl)methyl]amine,

5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methoxyphenol,

4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol,

3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-4H-chromen-4-one,

N-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N-[(4-Chloro-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-{[1-(4-methylbenzyl)-1H-pyrazol-5-yl]methyl}amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(2-phenyl-1H-imidazol-4-yl)methyl]amine,

N-[(2-Chloro-3-quinolinyl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(6-methyl-2-pyridinyl)methyl]amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-quinolinylmethyl)amine,

[5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-furyl]methyl acetate,

4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-pyridinylmethyl)amine,

5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol,

N-[2-(tert-Butylsulfanyl)benzyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-ethylbenzyl)amine,

5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxybenzoic acid,

N-(1,3-Benzodioxol-4-ylmethyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(1,3-thiazol-2-ylmethyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-ethyl-2-furyl)methyl]amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-quinolinylmethyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-quinolinylmethyl)amine,

5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxy-3-methoxybenzoic acid,

N-[(4-Bromo-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,

2-[2-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6-methoxyphenoxy]acetic acid,

N-[(4-Bromo-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-iodobenzyl)amine,

3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6,7-dimethyl-4H-chromen-4-one,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-isopropoxybenzyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-methylbenzyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-pyridinylmethyl)amine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2,4-dimethylbenzyl)amine,

Ethyl 5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methyl-3-furoate,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-furamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]butanamide,

2-{[5-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-6-methoxy-4-quinolinecarboxamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-furyl)-4-quinolinecarboxamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butanamide,

3-(1,3-Benzothiazol-2-ylsulfanyl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3,5-dimethoxyphenyl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-methoxyphenyl)acetamide,

2-[5-Chloro-2-oxo-1,3-benzothiazol-3(2H)-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]acetamide,

2-(1-Benzothiophen-3-yl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(3,4-dimethoxyphenyl)butanamide,

5-Cyclohexyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]pentanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-fluoro-2-methylbenzamide,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(1-phenylethyl)phthalamide,

2-Cyclopentyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

4-Chloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-nitrobenzamide,

2,2-Dichloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1-methylcyclopropanecarboxamide,

tert-Butyl 4-[5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}carbonyl)-2-methoxyphenyl]-1-piperazinecarboxylate,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-1-(2-thienylmethyl)-3-pyrrolidinecarboxamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[2-oxo-1,3-benzoxazol-3(2H)-yl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-fluorobenzamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-methylbenzamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-methylbenzamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(hydroxymethyl)benzamide,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-{2-[(methylsulfanyl)methyl]-4-pyrimidinyl}-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[5-methoxy-2-(methylsulfanyl)-4-pyrimidinyl]-1,2-ethanediamine,

2-({4-[(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)amino]-2-pyrimidinyl}amino)-1-ethanol,

N~4~-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-6-methyl-2,4-pyrimidinediamine,

N~4~-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N~2~,6-dimethyl-2,4-pyrimidinediamine,

2-Chloro-N~4~-cyclopropyl-N~6~-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-4,6-pyrimidinediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(4-phenyl-2-pyrimidinyl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(trifluoromethyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(propylsulfanyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~2~-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N~4~,6-dimethyl-2,4-pyrimidinediamine,

N~4~-Cyclopropyl-N~2~-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-2,4-pyrimidinediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(3-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(3-thienyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-[4-(2-thienyl)-2-pyrimidinyl]-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(1H-purin-6-yl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(5-methylthieno[2,3-d]pyrimidin-4-yl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(7-methylthieno[3,2-d]pyrimidin-4-yl)-1,2-ethanediamine,

N~1~-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N~2~-(9-methyl-9H-purin-6-yl)-1,2-ethanediamine,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-{[5-(trifluoromethyl)-2-pyridinyl]sulfanyl}acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-5-phenylpentanamide,

2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(phenylsulfanyl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine,

2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}-N-(3-methoxyphenyl)acetamide, dihydrochloride salt,

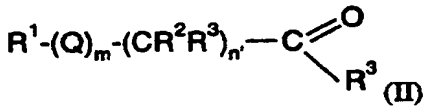
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3,4-dichlorophenyl)urea,

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3-methoxyphenyl)urea, and

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methoxybenzyl)amine, dihydrochloride salt.

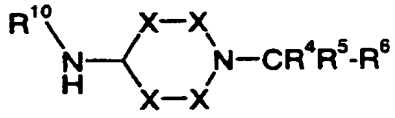
6. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

(a) when n is at least 1, the CR^2R^3 group attached directly to T is CHR^3 and T is NR^{10}, reacting a compound of general formula



(II)

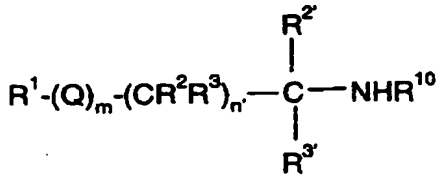
wherein n' is 0 or an integer from 1 to 3 and R^1, R^2, R^3, m and Q are as defined in formula (I), with a compound of general formula



(III)

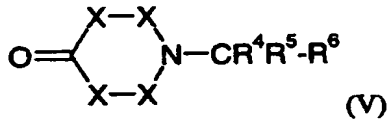
or a salt thereof, wherein X, R^4, R^5, R^6 and R^{10} are as defined in formula (I), in the presence of a reducing agent; or

(b) when n is at least 1, the CR^2R^3 group attached directly to T is $C(C_1\text{-}C_4 \text{ alkyl})_2$ and T is NR^{10}, reacting a compound of general formula



(IV)

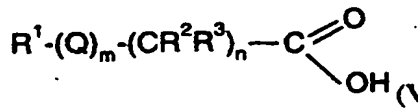
wherein n' is 0 or an integer from 1 to 3, $R^{2'}$ and $R^{3'}$ each independently represent a $C_1\text{-}C_4$ alkyl group, and R^1, R^2, R^3, R^{10}, m and Q are as defined in formula (I), with a compound of general formula



(V)

wherein X, R^4, R^5 and R^6 are as defined in formula (I), in the presence of a reducing agent; or

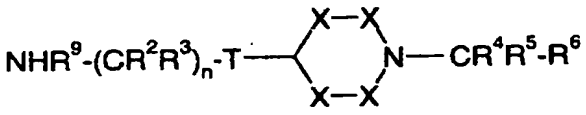
(c) when T is $C(O)NR^{10}$, reacting a compound of general formula



(VI)

wherein R^1, R^2, R^3, Q, m and n are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

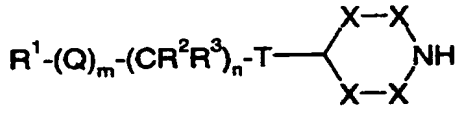
(d) when m is 1 and Q is NR^9, reacting a compound of general formula (VII), R^1 - L^1, wherein L^1 represents a leaving group and R^1 is as defined in formula (I), with a compound of general formula



(VIII)

or a salt thereof, wherein n, T, X, R^2, R^3, R^4, R^5, R^6 and R^9 are as defined in formula (I); or

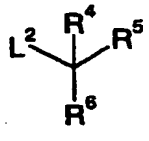
(e) when at least one of R^4 and R^5 represents a hydrogen atom, reacting a compound of general formula



(IX)

or a salt thereof, wherein R^1, R^2, R^3, Q, m, n, X and T are as defined in formula (I), with a compound of general formula (X), R^6 - C(O) - R^{20}, wherein R^{20} represents a hydrogen atom or a C_1-C_4 alkyl group and R^6 is as defined in formula (I), in the presence of a reducing agent; or

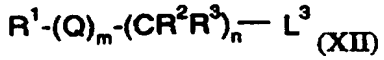
(f) reacting a compound of formula (IX) as defined in (e) above, with a compound of general formula



(XI)

wherein L^2 represents a leaving group and R^4, R^5 and R^6 are as defined in formula (I); or

(g) when T is NR^{10}, reacting a compound of general formula



(XII)

wherein L^3 represents a leaving group and R^1, R^2, R^3, m, n and Q are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

(h) when T is $NHC(O)NR^{10}$, reacting a compound of general formula

$$R^1\text{-}(Q)_m\text{-}(CR^2R^3)_n\text{—}\ N{=}C{=}O \qquad \text{(XIII)}$$

wherein R^1, R^2, R^3, Q, m and n are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above;

and optionally after (a), (b), (c), (d), (e), (f), (g) or (h) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained.

7. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

8. A process for the preparation of a pharmaceutical composition as claimed in claim 7 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 for use in therapy.

10. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4 in the manufacture of a medicament for use in therapy.

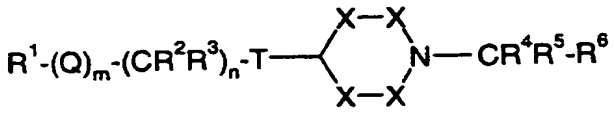
11. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective

amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 4.

ABSTRACT

NOVEL COMPOUNDS

The invention provides compounds of general formula



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, Q, m, n, X and T are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them, and their use in therapy, especially for the treatment of chemokine receptor related diseases and conditions.